Format for ANSWERING REVIEWERS

November 29, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name13272-review.doc).

Title: Oxidative stress: New insights on the association of non-alcoholic fatty liver disease and atherosclerosis
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Name of Journal: *WORLD JOURNAL OF HEPATOLOGY*

ESPS Manuscript NO: 13272

Please find enclosed the edited manuscript in Word format. The manuscript has been extensively reviewed following the suggestions of the Reviewers. In particular, we have introducted a new figure and amended the previous one. We have also added 27 new references. All changes have been highlited in red.
The paper has been also revised for overlap and similatities following the results of the cross chek performed by the Editor. All the relevant modifications have been done and overlapping text has been removed. All the references have been properly cited.
Despite the crosscheck allert, the follow references were already properly cited.

33 Bhatia LS, Curzen NP, Calder PC, Byrne CD. Non-alcoholic fatty liver disease: a new and important cardiovascular risk factor? *European heart journal* 2012; **33**(10): 1190-1200 [PMID: 22408036 DOI: 10.1093/eurheartj/ehr453]

52 Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. *The American journal of gastroenterology* 2004; **99**(8): 1497-1502 [PMID: 15307867 DOI: 10.1111/j.1572-0241.2004.30159.x]

54 Narasimhan S, Gokulakrishnan K, Sampathkumar R, Farooq S, Ravikumar R, Mohan V, Balasubramanyam M. Oxidative stress is independently associated with non-alcoholic fatty liver disease (NAFLD) in subjects with and without type 2 diabetes. *Clinical biochemistry* 2010; **43**(10-11): 815-821 [PMID: 20398645 DOI: 10.1016/j.clinbiochem.2010.04.003]

84 Munzel T, Gori T, Bruno RM, Taddei S. Is oxidative stress a therapeutic target in cardiovascular disease? *European heart journal* 2010; **31**(22): 2741-2748 [PMID: 20974801 DOI: 10.1093/eurheartj/ehq396]

109 Tome-Carneiro J, Gonzalvez M, Larrosa M, Yanez-Gascon MJ, Garcia-Almagro FJ, Ruiz-Ros JA, Tomas-Barberan FA, Garcia-Conesa MT, Espin JC. Resveratrol in primary and secondary prevention of cardiovascular disease: a dietary and clinical perspective. *Annals of the New York Academy of Sciences* 2013; **1290**: 37-51 [PMID: 23855464 DOI: 10.1111/nyas.12150]

113 Salamone F, Galvano F, Marino Gammazza A, Paternostro C, Tibullo D, Bucchieri F, Mangiameli A, Parola M, Bugianesi E, Li Volti G. Silibinin improves hepatic and myocardial injury in mice with nonalcoholic steatohepatitis. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2012; **44**(4): 334-342 [PMID: 22197629 DOI: 10.1016/j.dld.2011.11.010]

130 Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, Hazen SL, Feldstein AE. Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. *Hepatology* 2012; **56**(4): 1291-1299 [PMID: 22505276 PMCID: 3430813 DOI: 10.1002/hep.25778]

REVIEWER 1

1. Put the problem into clinical context

We added a discussion about the fact that diagnosis of NAFLD should increase attention on the cardiovascular risks factors. pag 4 line from 27 to 29

2. Address the main pathophysiologic mechanisms linking NAFLD to CVD

We addressed the main pathophysiologic mechanisms linking NAFLD to CVD in the new figure 2

3. Authors discuss imaging biomarkers of CAD but this part is not well embedded in the text. IMT and FMD are two only but of many risk factors. Moreover, IMT has an established role as an imaging biomarker whereas FMD remains related to the research laboratory. Please discuss.

Following the Reviewer's suggestion, we better introduced CAD biomarkers in the chapter.

6. Authors, in the light of their experience should give more clinical information on how to manage these patients, their risk stratification etc. A clinical algorithm would be very useful for the readership of the journal.

An algorithm (reported in new figure 1) about cardiovascular risk assessment and management has been added.

7. Figure 1 is too simplistic and useless in its present form.

Figure 1, now named figure 2, has been enriched with more details about the common pathophysiologic mechanism linking NAFLD to CVD

REVIEWER 2

The abbreviations need an accurate review

The abbreviations have been reviewed.

Figure-1 is useless

Figure 1 has been removed and two new figures have been introduced.

REVIEWER 3

2. The authors introduce the concept of NAFLD and the development of fibrosis; however: Apoptosis should also be described since it may trigger insulin resistance in patients.

As suggested, we added a discussion about the importance of the interplay between insulin resistance oxidative stress and apoptosis in NAFLD. We also add a new reference.

3. The description of the risks of small molecule supplementation is important.

We added a description of the potential risks of supplementation of Vitamin E. Page 10, lines 1-4.

4. Can the authors summarize the potential roles for: A. simultaneous supplementation using smaller doses of several small molecule antioxidants (Vitamin A, Vitamin E, Vitamin C, glutathione, etc); or B. simultaneous supplementation using a small molecule antioxidant with a trace element (zinc, copper, or selenium) that may increase expression of an enzymatic antioxidant.

Following the reviewers suggestion, we added a discussion about the potential use of simultaneous supplementation of small molecule antioxidants or small molecule antioxidants with a trace element. Page 10 lines 5-10.